# 2 Gender Issues in the Neurobiology of PTSD

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Posttraumatic stress disorder (PTSD) (American Psychiatric Association, 1994) is a relatively common psychiatric disorder, with an overall lifetime prevalence of about 8% in the general population (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). Rates of PTSD are significantly higher in certain at-risk populations, including combat veterans, victims of rape and violent assault (e.g., Kessler et al., 1995), and adolescents exposed to high levels of community violence (e.g., Lipschitz, Rasmusson, Anyan, Cromwell, & Southwick, 2000). In addition, despite common rates of exposure to traumatic events in males and females, the incidence and prevalence rates of PTSD are reported to be at least twice as high in women and adolescent girls as in men and adolescent boys (e.g., Breslau, Davis, Andreski, Peterson, & Schultz, 1997; Deykin & Buka, 1997; Stein, Walker, Hazen, & Forde, 1997; Stein, Walker, & Forde, 2000). The reasons for this gender difference in the incidence and prevalence of PTSD are not clear. As discussed in detail elsewhere in this volume, a number of factors could contribute to increased rates of PTSD in women, including gender-related differences in neurobiology.

In this chapter, we review published studies, as well as recent data from the National Center for PTSD, regarding the neurobiology of PTSD in women. The results of these studies then are compared to previous research findings in men with PTSD. This review provides, at best, leads about neurobiological factors that may contribute to gender differences in the vulnerability for PTSD. This is due to the fact that few studies with a neurobiological focus have been done on women with PTSD, and even fewer studies have compared neurobiological responses across gender. In addition, no published studies have investigated the effects of the menstrual cycle or re-

productive status on stress responsive systems in women with PTSD. Finally, methodological differences among previous studies of the neurobiology of PTSD make comparison across studies, as well as across gender, difficult.

This chapter therefore also reviews previous studies in *healthy* humans and animals that explore gender and reproductive hormone effects on stress-sensitive neurobiological systems. We hope this will provide clues about mechanisms that might increase the risk for PTSD in women. This is a challenging topic. Extensive research over the past 30 years has demonstrated that the effects of reproductive hormones on stress-sensitive systems are numerous and complex and, in some instances, gender- or species-specific. For example, estrogen appears to affect hypothalamic–pituitary–adrenal (HPA) function differently in men and women, while effects of gender on the serotonin system vary between humans and some strains of animals.

This suggests that if we really are to understand the neurobiology of PTSD in women, we must study women with PTSD—not men, and not female animals. However, research aimed at elucidating the neurobiology of PTSD has to this point focused largely on male populations, with studies in men and boys numbering over 40, where as studies in women or girls number less than 20. The reasons for this gender discrepancy in research focus are probably many and may relate in part to historical gaps in availability of money targeting research in women. For instance, the Veterans Administration, which has funded much of the past research into the neurobiology of PTSD, has focused its resources primarily on male combat veterans, because most veterans are men. Recently, though, money from public and private institutions supporting research on women has increased. The increased biological complexity of women compared to men also may contribute to the reluctance of researchers to study women. Sex hormone profiles associated with the menstrual cycle, pregnancy, and menopause have unique effects on most stress-responsive systems; thus, women must be studied in each of these states to gauge accurately the impact of stress. Short of this, research studies on women should *match* for menstrual cycle phase and hormone status. This renders clinical research on women more difficult, time-consuming, and costly. Therefore, this chapter also suggests changes in research and academic policy that may be needed to promote the execution of appropriately designed studies of the neurobiology of PTSD in women.

## PREVIOUS STUDIES OF THE NEUROBIOLOGY OF PTSD IN WOMEN

### The Catecholamines

Numerous studies completed over many years using a variety of methods have demonstrated hyperreactivity of the sympathetic and noradrenergic

systems in men with PTSD (Southwick et al., 1999). The sympathetic and noradrenergic systems mediate the "fight-or-flight" response activated in response to threat and accompanied by intense arousal, fear, aggression, and release of stress hormones such as cortisol. Indeed, it is generally appreciated that hyperreactivity of the sympathetic and noradrenergic systems contributes to the reexperiencing and hyperarousal symptoms of PTSD, as well as to the avoidance symptoms that develop in reaction to reexperiencing and hyperarousal symptoms. Consistent with these studies, Lemieux and Coe (1995) found increased 24-hour urinary norepinephrine and epinephrine levels in premenopausal women with PTSD compared to nonabused controls. Female subjects with a history of trauma, but without PTSD, showed values intermediate between these two groups. De Bellis et al. (1999) also found increased 24-hour urinary norepinephrine and dopamine levels in a combined group of girls and boys with PTSD compared to children with overanxious disorder and healthy controls. Urinary epinephrine levels were higher in the children with PTSD compared only to those with overanxious disorder. Because gender differences were not reported in the latter study, the most conservative interpretation of these studies is that females and males with PTSD are similar in having increases in the activity of the sympathetic or noradrenergic systems.

### *Gender-Related Hormone Effects*

Possible gender differences in the magnitude of the noradrenergic system changes in PTSD have not been well examined. In the study by De Bellis et al., (1999), boys with and without PTSD had greater 24-hour urinary norepinephrine and epinephrine levels than girls with and without PTSD. However, weight and body mass were not factored into this comparison, which is critical, because urinary norepinephrine levels increase with weight and body mass (e.g., Lemieux & Coe, 1995). Nevertheless, research in *healthy* subjects suggests that there are gender differences in the function of the noradrenergic system. In studies of students not explicitly screened for psychiatric illness, men were found to have greater urinary norepinephrine and epinephrine (e.g., Frankenhaeuser et al., 1978) responses to mental stress compared to premenopausal women, even when the analyses controlled for body weight.

The literature also suggests that fluctuations in reproductive hormones across menstrual phase and reproductive state in women influence sympathetic system reactivity (Figure 2.1). For instance, women in the luteal phase of the menstrual cycle have been shown to have increased norepinephrine levels (Goldstein, Levinson, & Keiser, 1983), increased stroke volume but lower vascular tone (Girdler, Pedersen, Stern, & Light, 1993), greater cardiovascular responses to a cold pressor test but not to mental arithmetic (Tersman, Collins, & Eneroth, 1991), and greater blood pressure and pulse changes in response to ambient environmental stress

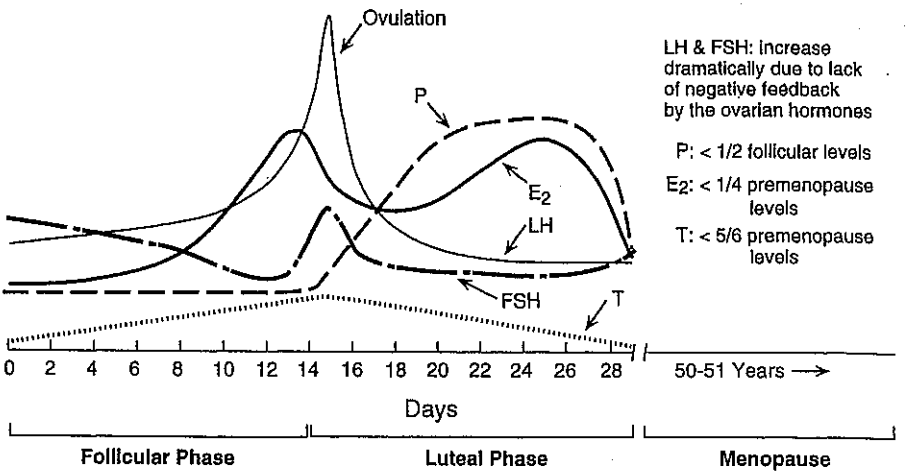


**FIGURE 2.1.** Reproductive hormone levels across the menstrual cycle and into menopause. Adapted from Carr and Wilson (1987). Copyright 1987 by the McGraw-Hill Companies, Inc. Adapted by permission.

(Manhem & Jern, 1994) than women in the follicular phase. Female sheep also have been shown to have greater norepinephrine and epinephrine responses to insulin-induced hypoglycemia during the luteal compared to the follicular phases of the estrus cycle (Komesaroff, Esler, Clarke, Fullerton, & Funder, 1998).

Nevertheless, estrogen levels within the luteal phase of the menstrual cycle have been found to correlate negatively with cardiac responses to stress (Sita & Miller, 1996), suggesting an inhibitory role for estrogen on sympathetic activity. Indeed, this is consistent with studies showing menopausal women to have increased cardiovascular and epinephrine responses (e.g., Saab, Matthews, Stoney, & McDonald, 1989) to mental stress compared to premenopausal women. In addition, Lindheim et al. (1992) and Komesaroff, Esler, and Sudhir (1999) reported that blood pressure and catecholamine responses to psychological stress were reduced by estrogen replacement in postmenopausal women.

Thus, if the degree of noradrenergic system hyperreactivity is considered important in mediating PTSD symptoms, menstrual phase and reproductive status should be factored into studies examining a role for the noradrenergic system in modulating PTSD risk and severity in women. On a technical note, we should also appreciate that there are more sophisticated measures of sympathetic system activity than urinary or plasma catecholamine measures, including determinations of jugular venous noradrenaline spillover and microneurography (Grassi & Esler, 1999). These

methods are reported to be more accurate and can be used to discriminate between brain noradrenergic and peripheral sympathetic activity. The use of these methods is illustrated in a recent study of panic disorder (Wilkinson et al., 1998), and could potentially be extended to studies of PTSD in men and women.

## Neuropeptide Y

Neuropeptide (NPY) is another sympathoadrenomedullary system neurotransmitter with probable relevance to the pathophysiology of PTSD in women. NPY, a 36-amino-acid peptide, is arguably the most abundant peptide in the peripheral and central nervous systems. NPY is stored (colocalized) with norepinephrine in most sympathetic nerve fibers involved in the mammalian fight-or-flight response. It is also present in nonadrenergic perivascular, gut, cardiac nonsympathetic, and parasympathetic nerves, as well as in the adrenal medulla (Wahlestedt & Reis, 1993). In the brain, NPY is colocalized with norepinephrine in the locus ceruleus, a brain area that mediates arousal. It is stored with a variety of other neurotransmitters in the amygdala, cortex, hippocampus, serotonergic raphe nuclei, and periaqueductal grey—also structures that play important roles in mediating the mammalian stress response (Heilig & Widerlov, 1990).

Extensive basic research has demonstrated that NPY is released when the sympathetic nervous system is intensely activated, as would be expected to occur in response to traumatic stress (e.g., Wahlestedt & Reis, 1993). Indeed, human plasma NPY levels have been shown to increase in response to activation of the sympathetic nervous system by intense exercise (Pernow 1986), electroconvulsive therapy (Richard Hauger, personal communication, March 2002), and the $\alpha_2$-noradrenergic receptor antagonist, yohimbine (Rasmusson, Hauger, et al., 2000). At the synaptic level, NPY has been shown to inhibit the release of neurotransmitters with which it is colocalized, as well as to enhance the postsynaptic receptor responses to these neurotransmitters once it is released (Colmers & Bleakman, 1994). Thus, NPY appears to play a role in enhancing the efficiency of the sympathetic nervous system by increasing the threshold for stress activation of the system and enhancing signal transduction once activation occurs.

Studies of the NPY effects in the central nervous system also suggest a role for NPY in the pathophysiology of anxiety disorders such as PTSD. Intracerebroventricular injection (i.e., injection into a cerebrospinal fluid compartment within the brain) of a low dose of NPY has been shown to increase anxiety in animals via activity at brain NPY-$Y_2$ receptors, whereas higher doses reduce anxiety via brain NPY-$Y_1$ receptors (e.g., Nakajima et al., 1998). Thus a dose-dependent balance between activation of central $Y_1$ and $Y_2$ receptors may determine how much anxiety is experienced in response to the stress-induced release of

NPY. In addition, intracerebroventricular administration of NPY has been found to antagonize anxiety produced by cortiocotropin-releasing factor (CRF) (Britton, Akwa, Spina, & Koob, 2000). CRF, a peptide, has been found to be involved in generating anxiety and defensive behaviors in response to stress in animals. In addition, high levels of CRF have been found in the cerebrospinal fluid of male combat veterans with PTSD (e.g., Baker et al., 1999).

A role for NPY in the pathophysiology of anxiety disorders in humans is also supported by observations of increased behavioral anxiety in animals showing decreased NPY messenger RNA (mRNA) levels in the amygdala and cortex after exposure to chronic restraint stress (Thorsell et al., 1998). In humans, anxiety has been shown to be increased in combat veterans with PTSD treated with the $\alpha_2$-antagonist, yohimbine (Southwick et al., 1993). These subjects with PTSD also showed low baseline plasma NPY levels and blunted NPY responses to yohimbine. In addition, there was a negative correlation between baseline plasma NPY levels and retrospective ratings of combat exposure, as well as activation of the sympathetic nervous system after yohimbine treatment (Rasmusson, Hauger, et al., 2000). These findings suggest that combat stress-induced decreases in plasma NPY may mediate long-term increases in the *reactivity* of the noradrenergic system in male veterans with PTSD. Indeed, these findings are consistent with animal research showing that plasma NPY decreases after chronic stress, and that these reductions are associated with increased stress activation of the noradrenergic system (Corder, Castagne, Rivet, Mormede, & Gaillard, 1992).

It is also important to note that a group of combat veterans without PTSD resembled combat veterans with PTSD in terms of decreased baseline plasma NPY. However, the combat controls showed normal NPY release and no increase in anxiety after yohimbine treatment, in contrast to PTSD subjects who exhibited reduced NPY release and elevated anxiety levels (Rasmusson et al., 2001). Thus, trauma-induced decreases in baseline NPY may increase sympathetic system reactivity, whereas maintenance of a normal capacity for NPY release in response to sympathetic nervous system stimulation may protect against the experience of pathological anxiety during stress. This possibility is supported by recent work showing that increases in plasma NPY levels are negatively correlated with dissociation (Morgan, Wang, et al., 2000) and distress (Morgan, Rasmusson, Wang, Hoyt, Hauger, & Hazlett, 2001) in male military recruits undergoing intensely stressful mock training interrogations. Further support for the impact of peripheral NPY responses on brain-mediated behavioral responses comes from the recent work of Antonijevic, Murck, Bohlhalter, Frieboes, Holsboer, and Steiger (2001) showing that the intravenous administration of NPY results in decreased nighttime ACTH and cortisol levels, as well as

enhanced stage 2 and total sleep. Indeed, as outlined in Table 2.1, trauma-induced alterations in NPY physiology could contribute to several comorbid conditions associated with PTSD.

It is therefore noteworthy that we also have preliminary data in premenopausal women with PTSD showing a decrease in baseline plasma NPY levels and blunted NPY release in response to adrenocorticotropic hormone (ACTH) (Rasmusson et al., 2001). Thus, trauma-induced changes in NPY levels, or altered NPY release, may also play a role in the pathophysiology of PTSD in women, although further research is needed to verify this role.

### *Gender-Related Hormone Effects*

Some research suggests that there may be a sexual dimorphism in the NPY response to stress. Male rats release more NPY in response to cold stress than female rats, and testosterone increases both tissue stores of NPY and NPY release (Zukowska-Grojec, 1995). These findings in rats are consistent with a study in humans showing increased exercise-induced NPY release in men compared to age-matched ovariectomized women with and without estrogen replacement (Zukowska-Grojec, 1995); indeed, testosterone levels in ovariectomized women are significantly reduced compared to levels in premenopausal women and men (Laughlin, Barrett-Connor, Kritz-Silverstein, & von Muhlen, 2000). Testosterone influences on NPY release also may account for the observed increase in exercise-induced NPY release in women in the immediate preovulatory phase of the menstrual cycle, when plasma testosterone levels in women peak (e.g., Lewandowski et al., 1998). In turn, relative decreases in NPY release during the luteal phase of the menstrual cycle may contribute mechanistically to increased norepinephrine levels observed in women during this phase (Goldstein et al., 1983).

Perhaps, then, hormone-based gender differences in NPY physiology could contribute to an increase in the rate of PTSD in women. Indeed, it seems conceivable that traumatic stress experienced during different phases of the menstrual or reproductive cycles could have different effects at a neurobiological level and thus could vary in its capacity to induce PTSD. Once chronic PTSD is established, PTSD symptoms also may vary across the menstrual and reproductive cycles in concert with changes in the capacity to restrain activation of the sympathetic nervous system by NPY. However, genetic factors may also play a role. A recently detected and relatively frequent variant in the structure of the NPY gene influences NPY release (Kallio et al., 2001) and thus might be expected to alter the adaptation of the NPY and sympathetic systems to chronic severe stress in affected individuals.

TABLE 2.1. Trauma-Induced NPY Deficits and Conditions Comorbid with PTSD

| Comorbid condition | How low NPY may contribute to comorbid conditions in PTSD |
|---|---|
| Decreases in hippocampal volume (Bremner et al., 1997; Stein, Koverola, et al., 1997) | NPY inhibits glutamate release in the hippocampus (Greber et al., 1994), whereas high glutamate and cortisol levels have been found to be toxic to hippocampal neurons by contributing to metabolic energy deficits during stress (Sapolsky, 1985, 1986; McEwen et al., 1986). |
| Memory dysfunction (Wolfe & Schlesinger, 1997) | NPY may enhance conditioned aversive memory but interfere with working memory (Flood et al., 1987). |
| Poor exercise tolerance (Shalev et al., 1990) | NPY is released in response to intense exercise and increases the efficiency of the sympathetic nervous system. |
| Chronic pain syndromes (Beckham et al., 1997) | NPY modulates transmission along pain fibers in the spinal cord (Walker et al., 1988; Mellado et al., 1996). |
| Sleep disturbance | Increased reactivity of the sympathetic nervous system due to low NPY levels in PTSD may inhibit rapid eye movement (REM) sleep onset and eventuate in compensatory increases in REM density and nightmares (Mellman et al., 1997). This is supported by animal data showing that NPY reverses both CRF and psychological stress-induced shortening of pentobarbital-induced sleep (Yamada et al., 1997) and influences circadian phase shifts (Biello et al., 1997). |
| Blunting of positive emotions (American Psychiatric Association, 1994) | NPY mediates reward when injected into the nucleus accumbens, an important brain reward center (Josselyn & Beninger, 1993). Low levels or low release of NPY in this area may contribute to the anhedonia observed in PTSD. |
| Nicotine dependence (Beckham et al., 1997; Shalev et al., 1990) | Nicotine induces NPY release from the adrenal gland. Thus, high rates of smoking among patients with PTSD and traumatized individuals without PTSD may represent attempts to compensate for NPY deficits induced by trauma exposure. |

## The Serotonin System

The serotonin system has been implicated in a range of biobehavioral phenomena of relevance to PTSD, including anxiety, aggression, impulsivity, sleep patterns, depression and suicidality, neuroendocrine regulation, perception, and cognition (Heninger, 1997). In addition, the selective serotonin reuptake inhibitors (SSRIs) have been found to be at least partially effective in the treatment of PTSD. This is consistent with findings of

serotonin system dysfunction in PTSD, including (1) decreased platelet paroxetine binding capacity and affinity, suggesting the possibility of deficient reuptake of serotonin after its release (e.g., Maes et al., 1999); (2) low platelet-poor plasma concentrations of serotonin (Spivak et al., 1999); (3) blunted prolactin response to fenfluramine, a serotonin releaser and reuptake inhibitor (Davis, Clark, Kramer, Moeller, & Petty, 1999); and (4) exaggerated reactivity to *m*-chlorophenyl piperazine (m-CPP), a serotonin 5-$HT_{2c}$ receptor agonist, as measured by increased anxiety, panic attacks, and other PTSD symptoms in a subset of male veterans with PTSD compared to nontraumatized, healthy controls (Southwick et al., 1997). Overall, these studies suggest that there may be a decrease in serotonin availability at baseline in PTSD, accompanied by an upregulation of postsynaptic 5-$HT_2$ receptors that eventuates in increased behavioral responses to stress-related phasic increases in serotonin release.

Unfortunately, no studies of the serotonin system have been undertaken in women with PTSD. However, recent literature suggests that gender-related differences in serotonin system function in healthy humans could contribute to women's increased vulnerability to PTSD.

### *Gender-Related Hormone Effects*

As discussed in detail by Rubinow, Schmidt, and Roca (1998) there are myriad effects of the gonadal hormones on all aspects of serotonin system function, including serotonin synthesis, release, reuptake, metabolism, receptor transcription, receptor number, receptor subtype, and receptor function. In addition, the serotonin system has been shown to be affected by gender, menstrual cycle phase, and reproductive state in numerous animal and human studies. However, some species-specific effects of the gonadal steroids on the serotonin system (e.g., Rubinow, Schmidt, & Roca, 1998) make it difficult to extrapolate findings from animal to humans studies. In this review then, we focus on studies of the serotonin system in humans.

In one study, Biver et al. (1996) demonstrated that there are fewer serotonergic 5-$HT_2$, receptors in women compared to men. Additionally, women have shown increased anxiety, prolactin, and oxytocin responses, as well as prolonged ACTH and cortisol responses to m-CPP, a serotonin 5-$HT_{2c}$ receptor agonist (e.g., Bagdy & Arato, 1998). This suggests that women may be more vulnerable to anxiety associated with stress-induced increases in endogenous serotonin acting at 5-$HT_2$ receptors. In addition, Nishizawa et al. (1997) used positron emission tomography (PET) to demonstrate decreased baseline rates of serotonin synthesis in the brains of women compared to men, as well as greater decreases in brain serotonin synthesis after tryptophan depletion. Thus, it has been suggested that inadequate increases in serotonin synthesis and the availability of this neurotransmitter in response to stress may increase the vulnerability of women to

depression. This may also pertain to PTSD. For example, serotonin restrains activation of the locus ceruleus (Charlety, Aston-Jones, Akaoka, Buda, & Chouvet, 1991), a brain area involved in regulation of arousal and attention (Aston-Jones, Rajkowski, & Cohen, 1999), and implicated in the pathophysiology of PTSD (Southwick et al., 1999).

Strong, recent evidence in both men and women indicates a link between neuroticism (anxiety, hostility, and depression) and a gene variant that codes for lower levels of the serotonin transporter involved in the reuptake of serotonin after its release. Interestingly, the relationship between this gene variant and neuroticism was more robust in a sample of primarily women compared to one containing primarily men (Greenberg et al., 2000). Thus, it is possible that effects of this serotonin transporter gene variant are influenced by gender or gender-related hormones. For instance, the number of serotonin transporters in the frontal lobe and brainstem is increased by estrogen (e.g., Sumner et al., 1999) and thus may vary across the menstrual cycle in women. Alternatively, a decreased capacity for serotonin synthesis in women may interact with a genetically based decrease in serotonin transporter number and affect serotonin system-mediated behavioral responses to stress.

Observed differences in serotonin system function between men and women also suggest that there may be gender differences in the responsiveness of patients with PTSD to psychotropic agents with serotonin system activity. Indeed, some, but not all, treatment studies of the SSRIs such as fluoxetine or sertraline suggest that women with PTSD may be more sensitive to their therapeutic effects (Hidalgo & Davidson, 2000). There also have been reports of the efficacy of atypical neuroleptics with a high ratio of serotonin 5-$HT_2$ to dopamine $D_2$ receptor antagonist activity, such as clozapine, risperidone, and olanzapine in PTSD (Friedman, 2000). However, studies of the efficacy of these agents in PTSD have focused on male populations, so we do not yet know how sensitive women with PTSD might be to their therapeutic effects. There may be gender differences in response to these agents given the lower number of brain 5-$HT_2$ receptors in women (Biver et al., 1996) and demonstrated effects of estrogen in upregulating 5-$HT_2$ receptor number (Sumner et al., 1999).

Thus, it is clear that studies exploring a role for the serotonin system in mediating the increased risk for PTSD in women are warranted.

### The Hypothalamic–Pituitary–Adrenal Axis

The hypothalamic–pituitary–adrenal (HPA) axis is activated in response to stress and leads to the release of cortisol from the adrenal gland. Cortisol, in turn, helps mobilize energy stores to fuel the fight-or-flight response, contains sympathetic noradrenergic responses, suppresses inflammation,

provides feedback to the brain to contain HPA axis activation, and has other brain effects that potentiate defense responses.

It is also important to note that high cortisol levels are thought to facilitate negative effects of stress on the structure and function of the hippocampus (e.g., Newcomer et al., 1999), locus ceruleus (Schulkin, Gold, & McEwen, 1998), and prefrontal cortex (e.g., Grundemann, Schechinger, Rappold, & Schomig, 1998), areas of the brain thought to play important roles in the production of symptoms and functional disabilities associated with chronic PTSD (e.g., Liberzon et al., 1999).

Thus, given the importance of the HPA axis in the mammalian responses to stress, there have been many investigations of HPA axis function in PTSD. However, few of these studies have focused on women. For this reason and others detailed later, it is difficult to make definitive gender-based comparisons of HPA axis function in PTSD at this time.

### *Tests of HPA Axis Reactivity*

A recent study of HPA axis function in premenopausal women with PTSD demonstrates increased ACTH and cortisol responses to CRF, as well as increased cortisol and dehydroepiandrostefone (DHEA) responses to ACTH, in the women with PTSD compared to nontraumatized comparison subjects (Rasmusson, Lipschitz, et al., 2001; Rasmusson, Zimolo, et al., 2001). In addition, there were significant positive correlations between both the cortisol responses to CRF and ACTH, and subjects' 24-hour urinary cortisol levels and cortisol responses to CRF and ACTH stimulation ($r$ = .47–.70, with $p < .05$–.001). These data are consistent with a recent report showing that women with major depression and early life stress have increased ACTH and cortisol responses when exposed to a laboratory psychosocial stress paradigm (Heim et al., 2000). Of note, 11 of the 14 women with major depression and early life stress had current PTSD, whereas the comparison group without depression contained only 5 women with PTSD.

These studies suggest that premenopausal women with PTSD may have increased pituitary and adrenal reactivity in response to novel psychosocial stress, as well as to exogenous administration of CRF and ACTH. This is consistent with studies in male veterans with PTSD showing increased plasma cortisol reactivity during 24-hour plasma sampling (Yehuda, Teicher, Trestman, Levengood, & Siever, 1996) and increased pituitary ACTH responses to metyrapone (Yehuda, 1997). Although the latter study has been interpreted to suggest the presence of enhanced glucocorticoid negative feedback in PTSD, it is possible that greater endogenous CRF stimulation of the pituitary, or greater pituitary sensitivity to endogenous CRF, contributed to the increased ACTH responses in the PTSD sub-

jects. This possibility is also supported by the work of Kaufman et al. (1997) showing a greater ACTH response to CRF among 13 depressed, abused children (8 with PTSD) compared to 13 depressed nonabused children (0 with PTSD) and 13 healthy controls. When the depressed, abused group was subdivided into high versus low ACTH responders, there was a trend for a greater number of subjects with PTSD to be among the high responders.

However, the findings of our CRF study in premenopausal women with PTSD contrast with a study by Smith et al. (1989) showing blunted ACTH and normal cortisol responses to CRF in 8 male veterans with PTSD, when compared to a group of 4 combat controls and 7 healthy, nontraumatized controls. It is possible that experimental confounds contributed to the findings by Smith et al. (1989). For instance, exposure to chronic stress affects HPA axis responses in healthy animals (Whitnall, 1994). Thus, combining small numbers of traumatized and nontraumatized controls into one healthy control group may not be an optimal methodological approach. In addition, psychotropic medications in that study were discontinued in male veterans with PTSD only 7 days before testing, and rates of smoking between study groups were not controlled. As outlined in Table 2.2, nicotine, antidepressants, neuroleptics, and anxiolytics can all have suppressive effects on HPA axis activity.

A recent study by Heim et al. (2000) has also produced findings unlike our results. In this study, women with childhood abuse and major depression (19/20 also had PTSD) showed lower absolute ACTH levels at 60 and 120 minutes after CRF treatment, and lower baseline and absolute cortisol levels at 5, 90, and 120 minutes compared to healthy subjects without childhood abuse. In contrast, a traumatized group without depression (4/20 subjects had PTSD) showed higher ACTH responses to CRF but lower cortisol levels at baseline and at 90 and 120 minutes after CRF treatment. During the ACTH study, the abused, depressed group showed only lower baseline cortisol levels, whereas the abused group that contained 4 subjects with PTSD showed lower cortisol levels at baseline and all time points after ACTH administration. These findings are difficult to interpret in terms of HPA axis findings in PTSD per se, because the presence of PTSD was not considered as a separate factor. However, it is possible that the presence of major depression or the severity of PTSD accounts for the different findings in the Heim et al. (2001) study. Indeed, half of the male patients with PTSD in the Smith et al. (1989) study also had major depression. However, methodological differences also make comparison of the findings difficult. In the Heim et al. (2001) study, the distribution of oral contraceptive users across groups was not reported, elapsed time since discontinuation of psychotropic medications was not reported, smoking was not ascertained, and nonabusive alcohol use by subjects during the study was allowed but not quantified. By comparison, in our recent study, smoking was matched

**TABLE 2.2. Experimental Factors to Control in Neurobiology Studies of PTSD**

| Experimental factor | Exposure | Effects on HPA axis | Authors |
|---|---|---|---|
| Antidepressants | Chronic | Decreased hypothalamic CRF, glucocorticoid receptors, plasma cortisol. | Brady et al. (1992) |
| | | Decreased urinary cortisol and ACTH responses to CRF. | Gold et al. (1995) |
| | | SSRI reduced cortisol response to ACTH. | Thakore et al. (1997) |
| Antipsychotics | Chronic | Restored dexamethasone suppression. | Tandon et al. (1991) |
| Benzodiazepines | Acute | Reduced extrahypothalamic CRF, increased hypothalamic CRF, reduced plasma ACTH. | Vargas et al. (1992) |
| Alcohol | Acute | Increased cortisol during the subsequent period of mild withdrawal. | Sarkola et al. (1999) |
| | Chronic | Decreased plasma cortisol, decreased pituitary CRF binding. | Yamada et al. (1997b) |
| | Dependence | Decreased cortisol reactivity up to 4 weeks after abstinence. | Costa et al. (1996) |
| Nicotine | Acute | Increased plasma cortisol. | Sellini et al. (1989); Spohr et al. (1980) |
| | Chronic | Increased baseline plasma cortisol and urinary cortisol excretion, decreased baseline plasma cortisol, and stimulated plasma cortisol. | Eliasson et al. (1993); Kirschbaum et al. (1994); Sellini et al. (1989); Krishnan-Sarin et al. (1999) |
| Adrenal 21-hydroxylase gene mutations | Rates vary from 1/3 to 1/16 depending on ethnic group | May decrease baseline but increase reactivity of ACTH, cortisol, and its progenitor neurosteroids. | Witchel et al. (1997); Witchell & Lee (1998); Merke et al. (1999) |

[a]Heterozygosity for 21-hydroxylase deficiency is frequent across all populations studied to date: 1/16 in a mixed Caucasian population, 1/3 in persons of Ashkenazi Jewish descent, 1/4 in Hispanics, 1/5 in Yugoslavians, 1/8 in Yupik Eskimos, and 1/10 in Italians (Witchel et al. (1997).

across groups, alcohol use was not allowed, subjects had been off of psychotropic medications for months to years, and reananlysis of the data excluding oral contraceptive users in the PTSD group did not alter the findings. Thus, it is clear from these studies that more work must be done to clarify the association between pituitary and adrenal reactivity patterns and PTSD in both genders.

Finally, it is interesting to note that our finding of increased DHEA release in response to ACTH in premenopausal women with PTSD is consistent with work by Lemieux and Coe (1995) showing increased 24-hour urinary 17-ketosteroid levels in premenopausal women with PTSD (17-ketosteroids are the metabolic products of DHEA). DHEA and its sulfated metabolite, DHEAS, cross into the brain, where they can act as positive modulators of the *N*-methy-D-aspartate (NMDA) receptor and as partial antagonists of the gamma-aminobutyric acid ($GABA_A$) receptor. In addition, oxygenated metabolites of DHEA may exert even more potent effects on brain function and behavior in brain regions such as the hippocampus (Rose et al., 1997). These compounds may affect regulation of other neurotransmitter systems thought to be involved in the generation of PTSD symptoms, increase anxiety, and influence memory or symptoms of dissociation (Chambers et al., 1999). Finally, DHEA, as well as progesterone, have antiglucocorticoid properties (e.g., Araneo, Shelby, Li, Ku, & Daynes, 1993). These compounds, therefore, could interfere with glucocorticoid negative feedback and potentially contribute to upregulation of the HPA axis in PTSD (Kudielka et al., 1998).

### *Dexamethasone Suppression Tests*

Previous studies have shown enhanced dexamethasone suppression of plasma cortisol in postmenopausal (Yehuda et al., 1995) and premenopausal (Stein, Yehuda, & Koverola, 1997) women with PTSD. Results of these two studies in women with PTSD largely agree with studies of dexamethasone suppression performed in males (Yehuda, 1997). However, it will be important to replicate these studies before firm conclusions can be drawn. For instance, hormone replacement therapy was not monitored among participants in the study of postmenopausal women. As discussed later, estrogen administration decreases brain and pituitary glucocorticoid receptors (Chrousos, Torpy, & Gold, 1998) through which the effects of dexamethasone are exerted. In addition, it would be important to control for menstrual cycle phase in dexamethasone studies in premenopausal women. Altemus et al. (1997) found that women in the luteal phase of the menstrual cycle are more resistant to dexamethasone suppression compared to women in the follicular phase. Whether this is due to antiglucocorticoid effects exerted by high levels of progesterone during the luteal phase is not clear.

### *24-Hour Urinary Free Cortisol Studies*

The only published study examining 24-hour urinary free cortisol levels in premenopausal women with PTSD demonstrated ~30% higher free cortisol levels in women with PTSD due to childhood sexual abuse compared to traumatized or nontraumatized controls (Lemieux & Coe, 1995). While this study has been criticized for the high free cortisol levels in all subjects, no other studies in premenopausal women have been published against which findings from this study can be compared. However, a recently presented study by Friedman, McDonough-Coyle, Jalowiec, Wang, Fournier, and McHugo (2001) also showed an approximately 30% increase in urinary free cortisol in 72 premenopausal and postmenopausal women with PTSD compared to 55 community controls, while Rasmusson, Lipschitz, et al. (2001) showed a trend for a 30% increase in the urinary free cortisol/creatinine ratio in women with PTSD in a small, underpowered study. Similarly, DeBellis et al. (1999) showed that girls and boys with PTSD had ~30% higher urinary free cortisol levels than healthy controls. In contrast, postmenopausal female Holocaust survivors with PTSD had ~30–50% lower urinary free cortisol levels than healthy, nontraumatized controls and Holocaust survivors without PTSD (Yehuda et al., 1995).

Several points must be kept in mind when interpreting the results of 24-hour urinary cortisol studies. First, 24-hour urinary free cortisol measurements reflect both baseline and reactive changes in plasma free cortisol levels. The female Holocaust survivors were confined to their homes during the study, whereas the women in our recent study and in the study by Lemieux and Coe (1995) were not. Thus, it is possible that the women and girls in the studies showing increased 24-hour urinary free cortisol levels in PTSD engaged in more physical activity or were exposed to more environmental provocations than the women in the study by Yehuda et al. (1995). If so, the effects of increased pituitary or adrenal reactivity, if characteristic of PTSD, would be more readily detected in the former two studies. It is also notable that the 24-hour urinary free cortisol levels in the Holocaust survivors correlated negatively with avoidance symptoms that in turn were very high in the survivors with PTSD. Prolonged active avoidance of traumatic reminders or employment of avoidant defenses (Mason, Wang, Yehuda, Riney, Charney, & Southwick, 2001) would be expected to minimize the frequency of stress-induced increases in ACTH, and thus may reduce trophic effects of ACTH on the adrenal gland. In time, this could reduce maximum adrenal cortisol responses to stress. Finally, a possible role for 21-hydroxylase deficiency heterozygosity should not be overlooked in producing low baseline cortisol levels in an ethnic group with high rates of functional 21-hydroxylase gene variants (see Table 2.2).

In addition, a number of other factors known to impact HPA axis function require attention in studies of 24-hour urinary free cortisol (Table 2.3). As noted in Table 2.3, differences in such factors may have contributed to the variable results of 24-hour urinary free cortisol studies in PTSD. The studies in which these variables were well controlled tended to show increased cortisol output in subjects with PTSD. In addition, no previous studies have attempted to quantify smoking rates among PTSD subjects and healthy controls. Because the prevalence and intensity of smoking is much higher among patients with PTSD and trauma controls compared to healthy, nontraumatized subjects (e.g., Beckham et al., 1997), nicotine use may have had significant unmeasured effects on the outcome of previous studies of HPA axis function in PTSD.

**TABLE 2.3. 24-Hour Urinary Cortisol in PTSD: Findings and Experimental Factors Controlled**

| | 4 weeks off medications | 4 weeks off EtOH[a]/drugs | Activity matched | Nicotine matched |
|---|---|---|---|---|
| Reduced cortisol output in PTSD | | | | |
| (Mason et al., 1986, male veterans; | No | No | No | No |
| Yehuda et al., 1990, male veterans; | No (2 weeks) | No | No | No |
| Yehuda et al., 1993, male veterans; | No | No | No | No |
| Yehuda et al., 1995, Holocaust survivors) | Yes | No? (EtOH?) | Yes | No |
| Cortisol output in PTSD not different | | | | |
| (Kosten et al., 1990, male veterans; | No | No | No | No |
| Mason et al., 2001, male veterans; | Yes | Yes | No | No |
| Baker et al., 1999, male veterans) | Yes | Yes | Yes | No |
| Increased cortisol output in PTSD | | | | |
| (Pitman & Orr, 1990, male veterans[b]; | Yes | Yes | Yes | No? |
| Lemieux & Coe, 1995, females; | No | Yes | Yes | No |
| Maes et al., 1998, male and female burn victims; | Yes | No? (EtOH?) | Yes | No |
| De Bellis et al., 1999, male and female children; | Yes | Yes | Yes | Yes |
| Rasmusson et al., 2001, females; | Yes | Yes | Yes | Yes |
| Friedman et al., 2001, females) | No | No | Yes | Yes |

[a]EtOH = ethanol.

[b]As male veterans with PTSD were compared to combat controls that have only somewhat lower rates and intensities of smoking (Shalev et al., 1990; Beckham et al., 1997), nicotine use was probably fairly well matched in this study.

### *Gender-Related Hormone Effects*

Most studies in animals suggest that the HPA axis is more reactive in females than in males (e.g., Galea & McEwen, 1999). However, studies of gender differences in HPA axis functioning in healthy humans have yielded mixed results. As reviewed by Kirschbaum, Kudielka, Gaap, Schommer, and Hellhammer (1999), men have consistently shown higher ACTH and free cortisol responses to laboratory-controlled psychosocial stress than women. Men also appear to have higher circulating ACTH levels than women. On the other hand, men and women have shown comparable ACTH responses to human CRF, whereas women have shown greater ACTH responses to ovine CRF, and greater adrenal sensitivity to ACTH (Kirschbaum et al., 1999).

The neurobiological mechanisms underlying these gender differences in HPA axis responses in humans are unknown. Gender differences in "threat appraisal" could certainly contribute to the differences in HPA axis responses to laboratory psychosocial stressors between men and women. This possibility is supported by studies showing that men and women modulate their ACTH and cortisol responses differently in response to the presence of persons providing social support during exposure to laboratory psychosocial stress (Kirschbaum, Klauer, Filipp, & Hellhammer, 1995). However, there may be a more direct role for "gender-associated" hormones such as estrogen, progesterone, and testosterone as well.

For instance, estrogen has been shown to increase HPA axis reactivity to stress in men and gonadectomized or intact male animals (e.g., Chrousos et al., 1998). Urinary and plasma cortisol levels are also greater in women with increased estrogen levels due to pregnancy or high-dose estrogen replacement (Lindholm & Schultz-Moller, 1973). In addition, De Leo, la Marca, Talluri, D'Antona, and Morgante (1998) showed decreased CRF-induced ACTH release in women 8 days after ovariectomy, when estrogen levels are markedly reduced. One means by which estrogen may increase HPA axis activity is by downregulating hypothalamic and pituitary glucocorticoid Type II receptors that mediate glucocorticoid negative feedback (Chrousos et al., 1998). There is also an estrogen response element located in the region of the CRF gene that promotes its expression (Vamvakopoulos & Chrousos, 1993). Thus, it has been suggested that the increased reactivity of the HPA axis to psychosocial stress in men may be explained by the conversion of high levels of free testosterone in men to estradiol by the brain enzyme aromatase (Kirschbaum et al., 1999).

However, more recent work suggests that physiological estrogen levels may suppress HPA axis activity in women. Young, Altemus, Parkinson, and Shastry (2001) found that physiological replacement of estrogen in ovariectomized animals decreases ACTH responses to restraint stress. In addi-

tion, Komesaroff et al. (1999) have shown that physiological estrogen dosing suppresses ACTH and cortisol responses to mental stress in perimenopausal women. While these results appear to contrast with those of De Leo et al. (1998), it is important to note that the latter study lacked control subjects exposed to surgical stress but not to ovariectomy. In addition, sex steroids other than estrogen, such as progesterone and testosterone, are reduced by ovariectomy. Indeed, testosterone levels after ovariectomy are below those of normal menopause (Laughlin et al., 2000). Finally, it is important to distinguish the perimenopause from menopause, as well as to control for the time elapsed after ovariectomy or menopause in studies examining effects of estrogen or other sex steroids in women. Sex steroid and other neurotransmitter receptor systems, exposed to decreasing levels of ovarian hormones for increasing amounts of time as menopause occurs, make progressive adjustments in their number and sensitivity. Thus, estrogen could have variable effects depending on whether it was administered early or late in menopause.

Whereas testosterone is generally thought to inhibit HPA axis reactivity (Handa, Burgess, Kerr, & O'Keefe, 1994), it also may play a role in producing the enhanced ACTH and cortisol responses to novel laboratory psychosocial stress in men compared to women. Viau, Chu, Soriano, and Dallman (1999) showed that testosterone is necessary for the normal increase of arginine vasopressin (AVP) in the hypothalamus of adrenalectomized rats; AVP, in turn, is responsible for potentiation of ACTH release in response to novelty in chronically stressed rats (Aguilera, 1998). Thus, it is interesting that DHEA responses to ACTH are significantly increased in women with PTSD (Rasmusson, Zimolo, et al., 2001). Because DHEA is an immediate precursor of testosterone, it is possible that both DHEA and testosterone increase brain neurophysiological responses to novelty in women and men with PTSD. This possibility thus suggests that research into a possible role for testosterone in altering HPA axis and brain functioning in women with PTSD is needed.

Finally, a role for progesterone in increasing HPA axis function should be investigated in women. As noted earlier, progesterone has antiglucocorticoid properties and thus may interfere with glucocorticoid feedback. This possibility is supported by several studies suggesting that HPA axis reactivity is increased during the luteal phase of the menstrual cycle, when progesterone levels are markedly elevated over levels in the follicular phase. Genazzani, Lemarchand-Beraud, Aubert, and Felber (1974) demonstrated higher morning ACTH and cortisol levels during the luteal phase of the menstrual cycle in five healthy subjects, whereas Stewart et al. (1993) demonstrated decreased baseline ACTH levels during the luteal phase. Kruyt and Rolland (1982) showed a higher cortisol peak 90 minutes after ACTH administration in women tested during the luteal phase of the menstrual cycle compared to those tested during the early follicular phase. Similarly,

Kirschbaum et al. (1999) found higher salivary free cortisol, but not plasma total cortisol, responses to ACTH and psychosocial stress during the luteal compared to follicular phases of the menstrual cycle. These results, in turn, may be consistent with work by Altemus et al. (1997) demonstrating decreased sensitivity to glucocorticoid negative feedback during the luteal phase.

Nevertheless, the relative lack of studies of HPA axis function in women with PTSD, the number of experimental confounds present in earlier HPA axis studies, and the lack of studies designed explicitly to examine gender differences in HPA axis function in PTSD make it difficult to know whether there are gender differences in adaptation of the HPA axis to traumatic stress. Future research within and between genders must therefore be done with care to control for menstrual phase and reproductive status, as well as other factors with impact on HPA axis function. Only then can we determine whether alterations in HPA axis adaptations to stress contribute to the higher risk for PTSD observed in women.

## Studies of Central and Peripheral Nervous System Structure and Function

There is emerging experimental evidence that women with PTSD, compared to healthy nontraumatized or traumatized controls, tend to have differences in certain types of brain-mediated abilities. For example, women with PTSD appear to exhibit (1) abnormalities in brain lateralization (Morgan, Grillon, Lubin, & Southwick, 1997); (2) increased preconscious sensitivity to changes in acoustical stimuli (Morgan & Grillon, 1999); (3) decreased conscious responses to target stimuli (Charles et al., 1995); (4) increased heart rate responses and changes in skin conductance in response to high-intensity tones, along with slower habituation of these responses; and (5) differences in blood flow in the frontal lobe and other brain areas measured by PET during the reading of personalized trauma scripts (e.g., Bremner et al., 1999).

Women with PTSD have been found to have decreases in hippocampal volume compared to healthy nontraumatized or traumatized controls (e.g., Bremner et al., 1997). They also have shown poorer performance on hippocampus-dependent cognitive tasks in one (Bremner et al., 1999), but not another (Stein, Hanna, Vacrum, & Koverola, 1999) study of explicit memory function in PTSD. It is not clear, however, whether women with PTSD have greater or lesser abnormalities in hippocampal structure or function than do men. It is also not yet clear to what extent women with PTSD, like men with PTSD, may be predisposed to the development of such abnormalities. Existing studies do not yet inform us as to whether these abnormalities are the product of traumatic stress exposure in vulnerable individuals or predate and possibly increase the risk

for PTSD—very important questions for understanding PTSD, as well as the role of gender in its development.

Nevertheless, it does seem likely that gender differences in the function of any one of the neurobiological systems discussed in the preceding sections could predispose women to the development and expression of such PTSD-related brain and peripheral nervous system abnormalities. For instance, cortisol, DHEA, NPY, serotonin, and the sex steroids all play roles in the production of stress-induced changes in hippocampal structure and function. These factors also influence the function of the frontal lobe, the amygdala, and other brain areas involved in the detection and interpretation of threat, as well as the coordination of physiological or behavioral responses to threat. Thus, future research should study the means by which PTSD-associated alterations in these neurotransmitter systems may translate into the neurophysiological, cognitive, and behavioral manifestations of PTSD. Information gleaned from these studies can then be used to guide the development of improved, symptom-specific psychological and pharmacological treatment strategies.

## FUTURE RESEARCH DIRECTIONS AND RESEARCH POLICY RECOMMENDATIONS

A number of methodological points should be considered in the design of future studies of the neurobiology of PTSD in women. For instance, past studies have often resorted to comparing women in either the follicular or the luteal phase of the menstrual cycle to men. However, there is no reason to think that the physiology of women in either the follicular or luteal phase of the menstrual cycle is more or less comparable to the physiology of men. Indeed, fluctuations in sex steroids across the menstrual cycle will have unique effects on neurotransmitter systems in women. In addition, sex steroids have gender-related prenatal and ongoing postnatal organizational and structural effects on the brain that persist despite the addition or subtraction of sex steroids during research studies. Therefore, we believe that parallel studies in men and women need to be conducted across developmental epochs to elucidate accurately differences in the neurobiology of PTSD between genders.

In such studies, women need to be carefully monitored for a variety of factors, including stage of menstrual cycle, oral contraceptive use, pregnancy, and menopause. Each of these states has a unique hormonal profile that may differentially affect immediate and long-term adaptations to traumatic stress. Indeed, as previously suggested by Saxe and Wolfe (1999) women may be more vulnerable to the development of PTSD during certain phases of the menstrual cycle or during different reproductive states. It is also possible that PTSD symptoms will vary across the menstrual cycle or

across reproductive states. Finally, it is possible that the efficacy of medications for PTSD will vary across gender, developmental epochs, menstrual cycles, and reproductive states. Therefore, more resources need to be directed toward the study of PTSD in women. For instance, the duration of longitudinal monitoring of women in such studies may need to be lengthened to allow more time for the study of women across the stages of the menstrual cycle, as well as to allow for the recruitment of a greater number of control groups.

More attention also needs to be directed toward research in prepubertal and pubertal girls and boys exposed to trauma. Indeed, several studies have found very high rates of PTSD and partial PTSD among inner-city girls exposed to community trauma (e.g., Lipschitz et al., 2000). We thus need to address the larger socioeconomic context in which community trauma occurs and understand the spectrum of neurobiological and psychosocial factors that potentially increase the risk for PTSD among exposed children. For instance, the production of adrenal neurosteroids, such as DHEA, rises steeply at adrenarche (Genazzani, Bernardi, Monteleone, Luisi, & Luisi, 2000), a period of time before the onset of actual puberty, when adrenally derived steroids increase and induce the development of secondary sex characteristics. DHEA levels continue to rise until adulthood. Therefore, this steroid may play very different roles in the mediation of traumatic stress effects on the brain and HPA axis before and after adrenarche, and may differentially impact boys and girls. We also need to devise interventions that can alter the long-term deleterious psychiatric and psychosocial outcomes of trauma exposure in female children. For instance, Lipschitz et al. (2000) found PTSD symptoms in inner-city girls to be associated with depression, school failure, trouble with the law, smoking, and marijuana use.

Indeed, another important area for future research will be understanding how trauma, PTSD, and substance abuse disorders are interrelated. Interestingly, alcohol withdrawal in animals has been found to cause changes in brain CRF and other neurobiological factors similar to those seen after traumatic stress (Koob, 1999). Traumatic stress and PTSD, in turn, appear to be associated with neurobiological changes that predispose patients to substance abuse. Traumatic stress-induced reductions in NPY levels and/or release may be one such factor. Mice with genetically determined increases in alcohol consumption have lower brain levels of NPY, and mice with genetically engineered NPY deficits consume increased amounts of alcohol. Conversely, transgenic mice with increased brain NPY levels consume less alcohol and are more sensitive to its sedative effects (Thiele et al., 1998). We hope that further research exploring these relationships will lead to better ways to prevent or break the vicious cycle between trauma or chronic stress and substance abuse. This will be especially important for women in substance abuse treat-

TABLE 2.4. Differences in Stress System Responses between Menstrual Phases, Reproductive States, and the Sexes in Healthy Subjects

| | Luteal phase versus follicular phase | Menopause versus premenopause | Women versus men |
|---|---|---|---|
| Sympathetic noradrenergic system | Increased norepinephrine (NE) levels<br>Increased stroke volume/lower vascular tone<br>Increased cardiovascular responses to cold pressor test<br>Increased cardiovascular responses to environmental stress<br>Higher estrogen levels are associated with decreased cardiovascular responding during the luteal phase | Increased cardiovascular responses to mental stress compared to menopausal women; responses are rectified by estrogen replacement | Decreased norepinephrine and epinephrine responses to mental stress |
| NPY | Decrease NPY release during exercise compared to the periovulatory follicular phase | | Female animals release less NPY in response to the cold pressor test<br>Testosterone increases tissue stores and release of NPY<br>Decreased NPY release during exercise in postmenopausal women compared to age-matched men |
| Serotonin system | Effects of the menstrual and reproductive cycles have not been examined | | Fewer serotonin 5-HT receptors<br>Increased anxiety, prolactin, and oxytocin responses to the 5-HT agonist, m-CPP<br>Decreased rates of 5-HT synthesis |
| HPA axis | Decreased cortisol suppression by dexamethsaone<br>Increased cortisol responses to ACTH stimulation<br>Increased cortisol responses to psychological stress | | Decreased cortisol responses to the Trier Social Stress Test<br>Similar responses to human CRF<br>Prolonged responses to ovine CRF<br>Increased cortisol release to ACTH |

ment, who have significantly higher rates of trauma exposure than men (e.g., Najavits, Weiss, & Shaw, 1997).

Finally, genetic factors may predispose individuals to the development of PTSD or contribute to differences in the rates of PTSD across ethnic groups. Such genetic factors may become magnified in their impact by interacting with gender-specific hormonal milieus. The identification of such factors could help guide early detection and more rapid implementation of preventive or treatment approaches.

## SUMMARY

As indicated in this chapter, it is not yet clear how the pathophysiology of PTSD differs between men and women. Indeed, the results of previous studies suggesting gender differences in the neurobiology of PTSD may, in part, have been influenced by differences in experimental design. However, it should also be clear that gender-related hormones, as well as hormone status within gender, influence stress-responsive systems of relevance to PTSD and probably influence short- and long-term neurophysiological adaptations to traumatic stress (summarized in Table 2.4).

Thus, future research should explore the role that such hormones may play in mediating the increased risk for PTSD in women. In addition, whereas in this chapter we suggest the importance of investigating gender differences in the noradrenergic, NPY, serotonergic, and HPA axis systems in PTSD, numerous other neurotransmitter and neuropeptide systems involved in the mediation of stress and stress-related psychiatric disorders also bear investigation. Indeed, it is possible that studying the neurobiology of PTSD in women, a group in which the neurobiological effects of trauma appear to be exaggerated, may not only help us to understand and treat PTSD in women but also may facilitate our understanding of the pathophysiology of PTSD in general.

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